Physical Training and Baroreceptor Control of Sympathetic Nerve Activity in Humans

Guido Grassi, Gino Seravalle, David A. Calhoun, Giuseppe Mancia

Abstract In nine sedentary subjects (16.5±0.4 years, mean±SEM) we measured blood pressure (Finapres device), heart rate (electrocardiogram), and postganglionic muscle sympathetic nerve activity (microneurography from the peroneal nerve) at rest and during intravenous infusion of phenylephrine and nitroprusside. These measurements were performed before and after 10 weeks of endurance training (2 h/d, 5 d/wk) that increased maximum oxygen consumption from 34.8±2.1 to 40.4±1.8 mL/kg per minute (P<.02). Basal mean blood pressure and muscle sympathetic nerve activity were lower after than before endurance training (97.5±1.8 versus 98.5±2.6 mm Hg, P<.05, and 14.0±1.8 versus 21.2±2.3 bursts per minute, P<.02), and the changes in these variables were closely related (r= .95, P<.01). Similar mean blood pressure increases induced by phenylephrine caused greater reductions in heart rate and muscle sympathetic nerve activity after than before endurance training (−8.6±0.8 versus −6.1±1.1 beats per minute, P:NS, and −78.0±4.6% versus −53.6±4.8%, P<.05). Likewise, similar mean blood pressure reductions induced by nitroprusside caused greater increases in heart rate and muscle sympathetic nerve activity after than before endurance training (18.6±3.0 versus 12.4±2.4 beats per minute, P<.05, and 128.1±26% versus 63.2±11%, P<.02). No alteration in hemodynamics, oxygen consumption, muscle sympathetic nerve activity, and baroreceptor reflex sensitivity occurred in four other age-matched sedentary subjects studied before and after a 10-week observation period without endurance training. These data provide evidence that endurance training markedly lowers sympathetic nerve traffic. This is accompanied by potentiation of the baroreceptor-sympathetic reflex, and this effect is more evident than that on baroreceptor vagal cardiac control. (Hypertension. 1994;23:294-301.)

Key Words • physical education and training • heart rate • baroreceptors • autonomic nervous system

The influence of endurance training (ET) on sympathetic tone in humans has been studied by measuring the effect of ET on plasma norepinephrine concentration, plasma norepinephrine spillover, and power spectral analysis of the heart rate variability. Such studies have led to the observation that ET is associated with an overall reduction in sympathetic tone.1 2 However, a reduction in sympathetic tone is limited to some regional circulations3 and no change in sympathetic activity has also been reported.10-12 Limited information is available on the effect of ET on direct recording of sympathetic nerve traffic by microneurography.13-15 This represents an important limitation because, although less suited than the norepinephrine spillover method in providing absolute steady-state values for sympathetic activity, direct recording allows a more dynamic estimation of the ongoing sympathetic drive, thereby allowing precise quantification of the sympathetic responses to alterations in the baroreceptor signal.

In the present study we have addressed this issue by systematic use of microneurography in normotensive subjects before and after a controlled program of ET. We have taken advantage of the continuous assessment of sympathetic activity provided by microneurography to also investigate the effect of ET on the baroreceptor-sympathetic reflex. Although highly relevant to the training-induced changes in sympathetic tone, this effect has not been previously investigated, the information available being limited to the effect of training on the baroreceptor modulation of the sinus node,16-22 ie, on a modulation largely dominated by the vagus.23-26

Methods Our study was started in 16 sedentary students, but because of three dropouts during the training procedure (see below), the study was completed in only 13. These 13 subjects (12 males, 1 female) had a mean age of 17.5±0.7 years (±SEM; range, 15 to 24 years) and were healthy and normotensive (arterial blood pressure <140/85 mm Hg on repeated screening measurements), with no family history of hypertension. No subject was overweight, and body mass index was always less than 25 kg/m² (mean, 21.3±1.0 kg/m²). The study protocol was approved by the Ethics Committee of our institution. All subjects agreed to participate after being informed of the study nature and purpose.

Hemodynamic, Microneurographic, and Echocardiographic Measurements Arterial blood pressure was measured by a finger photoplethysmographic device (Finapres 2300, Ohmeda) capable of providing accurate and reproducible beat-to-beat systolic and diastolic values.27,28 Resting blood pressure was also measured by a mercury sphygmomanometer, taking the first and fifth Korotkoff sounds as identification of systolic and diastolic values, respectively. Heart rate was monitored by a cardiotachometer triggered by the R wave of an electrocardiographic lead. Multunit recording of efferent postganglionic sympathetic nerve activity to the muscle bed (MSNA) was obtained from a
TABLE 1. Effects of 10 Weeks of Endurance Training on Baseline Data, Oxygen Consumption, and Work Capacity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>After 10 Weeks of ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>59.8±1.6</td>
<td>59.1±1.7</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²</td>
<td>111.6±4.2</td>
<td>119.0±6.3</td>
</tr>
<tr>
<td>Maximum work capacity, W</td>
<td>200.1±14.0</td>
<td>249.5±12.0*</td>
</tr>
<tr>
<td>Oxygen consumption at rest, (mL/kg)/min</td>
<td>3.65±0.22</td>
<td>4.13±0.2†</td>
</tr>
<tr>
<td>Maximum oxygen consumption, (mL/kg)/min</td>
<td>34.8±2.1</td>
<td>40.4±1.8*</td>
</tr>
<tr>
<td>Sphygmomanometric blood pressure, mm Hg</td>
<td>136.3±2.9/83.5±2.0</td>
<td>124.8±3.1/75.4±2.7*</td>
</tr>
</tbody>
</table>

ET indicates endurance training. Values are mean±SEM.
*P<.02, †P<.05, vs control.

microelectrode directly inserted into the right or left peroneal nerve posterior to the fibular head as previously described.13,29,30 The microelectrode was made of tungsten and had a diameter of 200 μm in the shaft, tapering to a 1- to 5-μm uninsulated tip. A reference electrode positioned subcutaneously 1 to 3 cm from the recording electrode served as ground. The nerve signal was amplified x70 000, fed through a band-pass filter (700 to 2000 Hz), and integrated with a custom nerve traffic analysis system (Bioengineering Department, University of Iowa, Iowa City). Integrated nerve activity was monitored by a loudspeaker, displayed on a storage oscilloscope (model 511A, Tektronix), and recorded, together with blood pressure, heart rate, and respiratory movements (strain-gauge pneumograph), on a model 3800 RS paper recorder.

Fig 1. Line graphs show systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), and muscle sympathetic nerve activity (MSNA, expressed as bursts per minute [bs/min] and bursts per 100 heartbeats [bs/100hb]) before (B) and at the end of (A) 10 weeks of physical training in nine subjects. Data are shown as individual and mean values. Asterisks (*P<.05, **P<.02) refer to statistical significance between mean values obtained before and at the end of the endurance training program.
Fig 2. Traces show original recordings of muscle sympathetic nerve activity (MSNA), blood pressure (BP), and heart rate (electrocardiogram [EKG] tracing) from one subject before and at the end of 10 weeks of physical training. MSNA, BP, and EKG tracings are shown for the control period and during phenylephrine (PHE) and nitroprusside (NTP) infusions.

The criteria outlined in previous articles for acceptance of MSNA recording were achieved in all subjects.13,20 Sympathetic bursts were identified by inspection of the mean voltage neurogram. Resting MSNA was calculated as bursts per minute and bursts per 100 heartbeats. Changes in MSNA induced by baroreceptor stimulation and deactivation were calculated as absolute and percent changes of integrated muscle sympathetic activity (bursts per minute times mean burst amplitude expressed in arbitrary units).

Quantification of sympathetic nerve traffic by the above-mentioned methods has been shown to differ by no more than 5% when done on the same tracing on two separate occasions by a single observer.29 The baroreceptor modulation of sympathetic activity was studied by the vasoactive drug infusion technique.23 Briefly, phenylephrine was infused incrementally into an antecubital vein at 0.3, 0.6, and 0.9 mcg/kg per minute, each step lasting 5 minutes. Nitroprusside was also infused incrementally into an antecubital vein for three periods of 5 minutes at 0.4, 0.8, and 1.2 mcg/kg per minute. The drug infusions were made in a random order and separated by an interval of 45 minutes. Mean arterial pressure (diastolic blood pressure plus one third of the pulse pressure), MSNA, and heart rate were averaged for the 10 minutes before phenylephrine and nitroprusside infusion and for the final 3 minutes of each dose. Baroreceptor reflex modulation was estimated by calculating (1) the changes in mean arterial pressure induced by each dose of phenylephrine and nitroprusside, (2) the resulting absolute and percent changes in MSNA and absolute changes in heart rate, and (3) the ratio between MSNA or heart rate changes and mean arterial pressure changes for each infused dose of vasoactive drug.

A monodimensional echocardiogram under bidimensional control was obtained in each subject before and at the end of the training program (see below). Left ventricular mass index was calculated according to the Penn Convention formula.31

Training Procedure

The nine subjects included in the study and enrolled in the physical exercise program were young healthy subjects who had been recruited by a professional athletic team (Gruppo Sportivo SNIA, Milan) to undergo an exercise program and then be further evaluated for their athletic aptitude. The program consisted of a daily session of long-distance running lasting approximately 2 hours. During these 2 hours the subjects were asked to run on the athletic track for periods of 20 to 30 minutes separated by intervals of 10 to 15 minutes. The speed and duration of each run and the intervals between each run were individualized and increased during the training period according to the coach’s evaluation of the degree of training reached. The training session was repeated 5 days a week for 10 weeks under the supervision of a coach belonging to the professional athletic team. The remaining four subjects did not undergo an exercise program and maintained their initial sedentary lifestyle throughout the same time period, thus serving as controls.

Effectiveness of the training procedure was verified by measuring maximal oxygen consumption (VO2max) during a bicycle exercise test. Workload was increased by 25 W every 3 minutes, and oxygen consumption was quantified during the last minute of each step by measuring the oxygen content of the gas expired into a Tissot spirometer with an infrared analyzer (Servomex). VO2max was defined as the oxygen consumption seen (1) at the maximal exercise heart rate as defined by the formula 220 minus age and (2) at the workload at which the increase in oxygen consumption showed no further increment or a small increment (<150 mL/min) compared with the preceding workload.32 Data are expressed as
resting oxygen consumption (milliliters per kilogram per minute), $V_{O_2}^{max}$ (milliliters per kilogram per minute), and maximum work capacity ($W_{max}$, watts), ie, the maximal workload achieved during the exercise test. The same procedure was used in the four subjects who maintained a sedentary lifestyle.

**Protocol and Data Analysis**

In the untrained condition the subjects were taken to the laboratory in the morning. After a light breakfast they were fitted with the intravenous cannula and the various measuring devices and allowed to rest for 30 minutes in the supine position. Blood pressure, heart rate, respiratory movements, and MSNA were then continuously measured (1) during a first 10-minute basal state, (2) during one vasoactive drug infusion, (3) during a second 10-minute basal state, and (4) during infusion of the second vasoactive drug. A 45-minute recovery period was observed between the end of the first drug infusion and the beginning of the second one. The procedure was repeated after the 10 weeks of training. The second examination was performed after 48 hours from the last exercise session or after the 10-week observation period in the control subjects using in each individual the sequence of interventions used in the first examination. Both in the untrained condition and after the 10 weeks of training or observation, the exercise test and echocardiographic evaluation were performed after completion of the morning study.

Data were calculated by a single investigator unaware of the experimental design. Baseline blood pressure, heart rate, and MSNA values from individual subjects were averaged for the group as a whole and expressed as mean±SEM. This was done also for the changes in mean arterial pressure, MSNA, and heart rate induced by each dose of phenylephrine and nitroprusside. Comparisons between data obtained before and at the end of the training program were made by two-way ANOVA. The Spearman analysis was used to correlate changes in different variables. A value of $P<.05$ was taken as the level of statistical significance.

**Results**

Table 1 shows that after the ET program there was no significant change in body weight and left ventricular mass index but a significant increase in maximum work capacity, oxygen consumption at rest, and $V_{O_2}^{max}$ and a significant decrease in sphygmomanometric blood pressure values.

As shown in Fig 1, ET was associated with a small but significant reduction in finger systolic, mean, and diastolic blood pressures, with no significant change in heart rate. ET was also associated with a clear-cut and significant reduction in MSNA, when expressed as both bursts per minute and bursts per 100 heartbeats to
account for differences in heart rate values. The reductions in MSNA and mean blood pressure were positively related to each other ($r=0.95$, $P<0.01$).

The effects of nitroprusside and phenylephrine infusion on finger mean arterial pressure, heart rate, and MSNA are shown in the example of Fig 2 and in Figs 3 and 4. Infusion of nitroprusside at three incremental doses caused a progressive reduction in mean arterial pressure, a progressive increase in heart rate, and a progressive increase in MSNA, whereas infusion of

**Table 2. Effects of 10 Weeks of Observation on Baseline Data in Four Subjects Not Undergoing Endurance Training**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>After 10 Weeks of Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>62.1±2.0</td>
<td>62.4±2.1</td>
</tr>
<tr>
<td>Finger BP, mm Hg</td>
<td>134.5±3.4/85.3±4.7</td>
<td>132.8±3.7/84.4±3.6</td>
</tr>
<tr>
<td>Sphygmanometric BP, mm Hg</td>
<td>137.3±4.0/84.0±3.5</td>
<td>135.5±3.8/85.1±2.9</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64.8±3.9</td>
<td>65.7±3.8</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²</td>
<td>113.1±5.0</td>
<td>112.9±4.8</td>
</tr>
<tr>
<td>Resting MSNA, bursts/min</td>
<td>23.7±2.0</td>
<td>23.0±1.9</td>
</tr>
<tr>
<td>Maximum work capacity, W</td>
<td>188.3±16.0</td>
<td>191.5±20.0</td>
</tr>
<tr>
<td>Oxygen consumption at rest, (mL/kg)/min</td>
<td>3.5±0.3</td>
<td>3.6±0.3</td>
</tr>
<tr>
<td>Maximum oxygen consumption, (mL/kg)/min</td>
<td>34.0±2.4</td>
<td>33.5±2.5</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; bpm, beats per minute; and MSNA, muscle sympathetic nerve activity. Values are mean±SEM. No change in the various variables was statistically significant.
phenylephrine had opposite effects. The increase in heart rate and MSNA by nitroprusside was significantly greater after than before ET, and the difference in the ratio between heart rate or MSNA and mean arterial pressure changes, with the exception of the first dose, was always statistically significant. This was the case also for the reduction in MSNA induced by phenylephrine, whereas the phenylephrine-induced reduction in heart rate was greater after than before ET, but the difference did not achieve statistical significance.

There was no significant relation between the increase in baroreceptor reflex sensitivity associated with ET and the concomitant reduction in baseline finger mean arterial pressure and MSNA values.

The results obtained in the four subjects kept under 10-week observation without ET are shown in Table 2 and Fig 5. Briefly, baseline values were similar before and after the 10-week observation period without the training program. This was the case also for the baroreceptor reflex ratio estimated by stepwise phenylephrine and nitroprusside infusions.

**Discussion**

In our subjects ET was associated with a consistent and clear-cut reduction in sympathetic nerve traffic recorded from the peroneal nerve. This confirms the results of previous studies based on other methods for measuring sympathetic activity, such as plasma norepinephrine concentration, norepinephrine spillover, and power spectral analysis.\(^1,9\) It also suggests that the reduction in sympathetic activity originates from a central effect of training, ie, that the reduction in plasma norepinephrine induced by training is not accounted for by factors attenuating the release of this substance from nerve terminals but (at least in part) by an actual reduction in neural sympathetic discharge.

Our observations also provide new information on the effect of physical training on the baroreceptor reflex.

The following additional points should be discussed. First, as mentioned above, in some studies plasma norepinephrine and peroneal sympathetic nerve traffic were not found to be affected by training.\(^10,12,14,15\) The reasons for these negative results are not clear; however, previous studies on sympathetic nerve traffic were largely based on comparisons between trained and untrained subjects,\(^14,15\) and our experimental design made use of a more sensitive within-group comparison. This may be particularly important for muscle sympathetic nerve traffic that is characterized by large inter-
individual and small intrindividual variability. It may also be important that in our study the training program was heavier than that used in the studies mentioned above. Finally, whereas we studied postpubescent boys, the other two studies included men and women. Thus it is possible that the ability of physical training to reduce sympathetic activity depends on the intensity of the training procedure, age, and gender factors.

Second, in agreement with other reports in normotensive subjects, in our subjects training was associated with a slight but consistent reduction in arterial blood pressure. Interestingly, although the reduction in blood pressure was correlated with the decrease in sympathetic nerve traffic, neither phenomenon was related to the concomitant increase in the sensitivity of the baroreceptor-sympathetic reflex observed during ET. This may be interpreted as if the training-dependent reduction in blood pressure is sympathetically mediated, although previous observations that training-induced reduction in blood pressure precedes that of plasma norepinephrine are against this interpretation. It also suggests, however, that not all changes in sympathetic activity associated with physical training originate from potentiation of the baroreceptor reflex. We thus can speculate that central and/or other reflex functions participate in this phenomenon. One of them may be represented by the cardiopulmonary receptor reflex, although its potentiation by training procedures has not been unequivocally demonstrated.

Finally, some limitations of our study need to be emphasized. First, microneurography allows the examination of sympathetic activity to skeletal muscle circulation, and it is therefore impossible to know whether the recorded changes in nerve traffic reflect quantitatively the neural changes induced by physical training in other vascular districts. Second, because the vasoactive drug method may affect central venous pressure, it is impossible to exclude the possibility that our findings on the arterial baroreceptor reflex were not mediated to some extent by an involvement of the cardiopulmonary reflex. Finally, our conclusions apply to short-term, albeit intense, physical training and cannot be extrapolated to the neural effects of long-term training leading to structural cardiovascular alterations. Indeed, after several years of heavy physical exercise, professional athletes with marked left ventricular hypertrophy show an impairment of the cardiopulmonary receptor reflex and the baroreceptor control of heart rate, ie, a depression rather than an enhancement of reflex cardiovascular control.

Acknowledgments

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